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08 March 1999

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Dockets Management Branch (HFA-305)
Food & Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Sirs

RE: DOCKET NO. 98D-1195

Please find enclosed our comments on the draft guidance on bioanalytical methods validation for human studies, issued December, 1998. These comments are provided by myself on behalf of behalf of Pfizer Limited, Sandwich, UK. Comments on behalf of Pfizer Inc, Groton will be provided separately.

Thank you,

Yours sincerely

David C Muirhead
Manager

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DOCUMENT COMMENTS FROM PFIZER CENTRAL RESEARCH (UK)
Issued by D C Muirhead - 3 March 1999
BIOANALYTICAL METHODS VALIDATION FOR HUMAN STUDIES

GUIDANCE FOR INDUSTRY

Our comments on the document are as follows:-

Introduction

The guidance is stated to be applicable to GC and HPLC methods. This is not wide enough and in particular LCMS needs to be included, considering the role this technique now plays in bioanalysis. Additionally, there is a brief mention of the fact that the guidance applies to e.g. immunological techniques, but further guidance for these techniques is required.

Background section

We agree that for an assumed linear relationship between concentration and response linearity should be confirmed. However, there should be an allowance for methods which do not involve a linear response.

We have problems with the sentence 'The acceptability of analytical data corresponds directly to the criteria used to validate the method'. The object of the validation exercise should be to assess the performance of the assay. Having done so, it may be appropriate to apply criteria regarding the decision to accept the method as suitable for the intended use..

There appears to be some confusion with regards to what constitutes a major change to an assay system. For example, a change of pump is unlikely to be of significance. However, change of pH or mobile phase solvent ratio can have a profound effect on the chromatography.

Sample collection is outside the scope of the laboratory SOPs. However, there is no question that there should be appropriate documentation relating to corresponding procedures.

We propose the phases relating to assay performance monitoring should be sub-divided as:

i) Reference standard preparation
ii) Assay validation
iii) In study performance monitoring
iv) Pre study validation

The latter being an abbreviated validation which should be carried out if the assay has not been run for some time, or if there have been minor modifications. Following major modifications, a full re-validation should be implemented.

Reference Standard

Reference standards for new drug candidates are synthesised in limited quantities. These materials are purified and fully characterized. Due to limited bulk supplies it is unlikely that a master standard can be maintained for comparison with future lots. Any lot that is manufactured in the future will also be fully characterized before it can be used as an analytical standard. Is there any guidance on the degree of characterization required for internal standards?

Pre-study validation

It is stated that validation should include analytical method development and documentation. It is our view that it is very important to document assay development. However, formal validation of a method cannot commence until the procedures can be specified and this is not possible until completion of assay development. It is, therefore, important that the final work in the method development phase should include adequate checks on precision, sensitivity and linearity.

It is stated that the stability of quality control samples and analyte in spiked samples should be determined. We are unclear as to why two types of spiked samples are specified, QCs are spiked samples.

It is stated that biological matrix from 6 different sources should be checked for interference and that if more than 10% of the blank samples exhibit significant interference, additional matrix samples should be tested. Our view is that in this situation the method would be unsuitable and, therefore, would require modification to improve specificity, (this assumes that the interference is not actually due to carryover or contamination). We would also argue that controlling the conditions (dietary, concomitant medications, time of day etc) as is standard practice will diminish the chances of finding specificity problems that might arise during a study. We suggest that this be looked at on a case by case basis.

Since food effect studies are now common practice we recommend appropriate checks on the effect of lipaemia on extraction recovery

Linearity

It is stated that the calibration curve should be prepared using the same biological matrix as the intended samples and we agree that wherever this is possible it should be the case, however, there are situations which necessitate the use of a surrogate matrix, e.g. tissue assays.

Throughout it is assumed that an internal standard will be used. Increasingly, internal standards are not used. This is because increasingly no or only minimal sample preparation is required.

What is the basis for specifying that the blank response corresponding to the retention time of the analytes should be at least 5 times greater than any interference, why not 3 times?

Precision , Accuracy and Recovery

We feel it is currently inappropriate to use the term 'within day' or 'between day' since with increasing speed of analysis these days, it is quite common place to run more than 1 batch of samples per day, we prefer the term 'within/between batch'.

We would not use the term 'quality control samples' for a validation study, our preference would be to use 'validation samples'. This avoids, for example, the confusion which may result by specifying an LOQ QC.

It is stated that for each validation batch the control matrix used for spiking purposes should be obtained from a different source. In order to obtain sufficient volume for validation purposes, it is usually necessary to work with a pool of biological matrix, i.e. a mixture of material from different sources. What is the value of using different sources or different pools for each validation batch? It would be more constructive to request that absolute recovery is assessed, using matrix from several different sources and indeed we would recommend doing so.

It is stated that recovery may be as low as 50% to 60%. We would disagree and indeed argue that the extent of recovery is only of relevance (unless sensitivity is an issue) if it becomes inconsistent across the concentration range. We suggest that this test is removed.

Quality Control Samples

Why insist that the quality control samples be prepared from a stock solution separate to that used to prepare the calibration standards?

Why 3 batches of matrix rather than a pool? Provided sufficient sources of matrix are checked for potential interference (specificity) and extraction recovery this is not necessary.

Documentation

It is stated that the documentation for validation should include a description to stability studies and supporting data. We maintain that while the validation data will include some limited stability data, it is not viable to run a stability study until the method itself is validated and, therefore, we would always present the formal stability data as a separate protocol and report. We do agree, however, that certain very short term stability data, e.g. freeze thaw, should be included.

It is stated that reassays should be done in triplicate. This is rarely possible due to limited sample volume and it would not be ethical to collect a larger volume for this eventuality. Duplicate reassays should be acceptable.

We do not routinely provide20% of subject chromatograms to regulatory agencies, nor do we submit all SOPs and raw data. However, all chromatograms, raw data and SOPs are retained and will be available for provision to regulators on request. Are these requirements targeted to specific studies (BE/BA)? Most NDA submissions include 50 or more studies that generate pharmacokinetic data. It is suggested that a smaller subset example chromatography of subject chromatograms, QC's and standard calibrators be provided for a majority of studies. The requirement for 20% will increase the size of most analytical reports and make electronic submission more cumbersome for industry and the agency reviewer.

AIRMAIL

Pfizer

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